Post-fracture Rehabilitation Effects on Brain Function in Older People

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ABSTRACT

Background Deterioration of cognitive function is an underlying cause of older people's fractures. The purpose of this study was to evaluate electroencephalogram and cognitive function in patients hospitalized with fractures, both at admission (before intervention) and at the time of discharge (after intervention), to investigate the effects of rehabilitation on brain function.

Methods A total of 24 patients hospitalized with fracture due to a fall were enrolled in this study. All the subjects received 140 minutes of rehabilitation every day during hospitalization. Touch Panel-type Dementia Assessment Scale (TDAS) was used to test their cognitive function. In electroencephalography (EEG), the Neuronal Activity Topography (NAT) system was used to calculate the "Alzheimer's disease (AD) - normal controls (NLc) differential similarity" in sNAT, ie, a numerical index to show the proximity to AD or normal NLc.

Results There was no significant difference in the total TDAS score among subjects who were examined before and after intervention, but 12 subjects who were observed with deterioration of cognitive functionat at before intervention had a significant improvement in "word-recognition," a sub-item in TDAS ($P < 0.05$). In addition, the NAT analysis findings showed that the differential similarity in sNAT significantly approached the NLc pattern ($P < 0.05$).

Conclusion EEGs in patients with fractures resulting from a fall became more similar to NL patterns at the time of discharge. In addition, recent-memory function of patients who had decline in cognitive function improved.

Key words dementia; electroencephalography; fall; osteoporosis; TDAS

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Abbreviations: AD, Alzheimer's disease; ADL, Activities of Daily Living; EEG, Electroencephalography; NAT, Neuronal Activity Topography; NLc, normal controls; TDAS, Touch Panel-type Dementia Assessment Scale

Bone fractures in older people are often associated with osteoporosis which predisposes bones to breakage with even minor external force; vertebral fracture and hip fracture are good cases in point.[1–3] Within the bone, bone turnover continues endlessly to maintain a certain bone mass and strength; osteoclastic cells destroy old cells (bone resorption) while osteoblast cells produce new cells (bone formation). Older people with repetitive vertebral fractures are at risk for a hip fracture, resulting in mobility issues. This can not only progress to a bedridden state, but also has an adverse impact on life expectancy.[4–6]

A major etiology of fractures in older people is a fall. Deterioration of cognitive function has been reported to predispose people to falls.[7] Thus, patients with dementia, which is associated with impairment of executive function, visual-spatial cognitive function, and attentiveness are at higher risk for falls.[7–9] The odds ratio for hip fractures was also 2–3 times higher in patients with Alzheimer's disease (AD).[6, 7] Previous studies have reported that amyloid beta-peptide, which is considered to be the causative substance of AD, may play an important role in the onset of AD since it increases in the bone tissue in osteoporosis and activates osteoclastic cells,[10] and therefore that osteoporosis was a risk factor for dementia.[11] In other words, osteoporosis and deterioration of cognitive function will incur a decrease of Activities of Daily Living (ADL) and Quality of Life. Given these facts, evaluation of the major pathological conditions that can negatively affect a healthy life expectancy is extremely important in geriatric care.

Both patients with hip fracture and those with vertebral fracture undergo rehabilitation soon after admission to help them resume their ADL and return to their home and society as early as possible. Physical exercise is being promoted as an effective non-pharmacological approach to maintain and improve brain health[12]. Research in humans and rodents indicates that the hippocampus, a brain region important for memory formation, is particularly impacted by physical exercise. Expression and release of brain-derived neurotrophic factor, a growth factor known to promote functional and structural plasticity in the hippocampus, may enhance learning.[13] In a

Table 1. Demographic information of participants

Test item	Gender (F/M)	Age (y)	Length-of-stay (day)	Duration of Illness prior to Hospitalization (day)
Total	18/6	83.5 ± 5.8	66.0 (49.0–88.0)	23.5 (14.5–29.5)
Cognitive assessment	12/4	83.1 ± 5.0	66.0 (50.5–88.0)	21.0 (9.5–29.5)
Electroencephalography	14/3	83.6 ± 5.9	82.0 (65.0–89.0)	24.0 (15.0–31.0)

Data presented as means ± SD or median (Inter Quarter Range). F, female; M, male; y, years.

study using mice, it was confirmed that physical exercise activated acetylcholine and enhanced the growth of neutral stem cells, which led to the assumption that the human body may have the same system.[14] Acetylcholine alters transmission of information and the activity status within the cerebral cortex and plays an important role in the activity of brain network.[15] Brains can be said to be a huge network of nerve cells.

Electroencephalography allows us to observe brain function of the living humans in a non-invasive manner. Electroencephalogram (EEG) represent variations in potential in which neuronal activity plays a major role. Recently, Musha et al.[16] developed the Neuronal Activity Topography system (NAT). The NAT system is inexpensive, poses no risk of radiation exposure, needs no strong magnetic field, and provides information concerning early detection of AD and the progression of symptoms. Since temporal changes of EEG measured on the scalp reflect partial changes of neuronal activity in the brain, the electric potentials of EEG can be processed numerically to grasp the neuronal activity status.

In this study, we measured EEG and cognitive function, in patients hospitalized because of fracture caused by a fall, both at admission (before intervention) and discharge (after intervention), to investigate the effects of rehabilitation on brain function. We also investigated the relationship between cognitive function and brain function, during the process of recovery from fractures.

MATERIALS AND METHODS

Study design

This study was an open-labeled prospective interventional study.

Participants

A total of 24 patients (6 men and 18 women), who were 65 years old and under 99 years old and admitted to the convalescent rehabilitation ward of Medical Corporation Yukoukai Kaikeonsen Hospital between June 1st and October 31th, 2015, because of hip fracture or vertebral fracture caused by a fall, were enrolled. Key exclusion criteria were defined as follows: (i) patients whose fractures were caused by a strong external force; (ii) patients who had severe complications other than bone fractures; (iii) patients who had disturbance of consciousness like delirium; (iv) patients who had temperamental brain diseases affecting EEG; or (v) patients who were judged by doctor to be unsuited to participate in the study. No patients met the exclusion criteria. Included were 12 patients with hip fracture (3 men and 9 women) and 12 patients with vertebral fracture (3 men and 9 women), all of whom were successfully discharged to their homes when rehabilitation was over. A pre-interventional cognitive function test was conducted in 20 patients excluding 4 patients who could not be tested for reasons such as the patient's refusal. Of them, data analysis was conducted in 16 patients (age: 72–89 years) excluding 4 patients who could not be tested after intervention for reasons such as unexpectedly early discharge. For the same reasons, only 17 patients (age: 72–93 years) were available for the EEG (Table 1). This study was approved by the Institutional Review Board of Tottori University Faculty of Medicine (approval number: 2630). All the subjects were thoroughly informed of the objectives and methods of this study and submitted a written informed consent before enrollment.

Convalescent rehabilitation

Convalescent rehabilitation is a rehabilitation conducted intensely in the recovery period in which medical condition starts to stabilize, after getting out of acute period. Its main objective is to get patients to be able to go back home and to improve ADL.[17] All subjects received 140 minutes of rehabilitation per day during hospital stay. On average, more than 80% of rehabilitation during hospital stay was completed in all the subjects. The rehabilitation consisted primarily of exercise therapy to meet the individual's physical condition. Specialized training, such as sitting up, sitting down, standing up, and standing still, were provided to improve movements or maintain postures, as well as to improve the most basic physical ability focusing on movements using aids such as a wheelchair, a walker, or a stick.

Cognitive assessment

Touch Panel-type Dementia Assessment Scale (TDAS) was used for cognitive assessment.[18] It was developed by modifying the Alzheimer's Disease Assessment

Scale-cognitive subscale,[19] a scale to assess AD patient's cognitive function, and by equipping it with a touch panel system that enabled us to conduct a test in a shorter period of time (shortened from 60 mins to 20 mins) even without expert assistance. The following 9 test items were included: following a command, visual-spatial perception, accuracy of the order of a process, naming fingers, orientation, money calculation, object recognition, and reading a clock face (of a non-digital clock). A total score of zero was defined as perfect. More incorrect answers meant higher scores. When all answers were incorrect, the score was 101 pts. Urakami et al. defined a score of < 7 pts as normal cognitive function, based on their clinical experience.[20, 21] Therefore, in this study, we also chose 7 as the cut-off score for patients with possible cognitive impairment.

Electroencephalography

Using Neurofax EEG-1214 system (NIHON KOHDEN CORPORATION, Tokyo, Japan), EEGs were recorded with eyes closed in a relaxed state for 5 minutes with 21 electrodes placed according to the international 10–20 system. EEG data were analyzed using NAT for quantitative evaluation. NAT analysis allows imaging of brain function by detecting even very slight differences in brain activity using markers from an EEG frequency analysis.[16] A data set from subjects with normal cognitive function was designated as the normal controls (NLc) template group while a data set from patients carefully diagnosed with AD were designated as the template AD group to compare "AD-like characteristics" of the subjects.[22, 23]

The sNAT markers were used for NAT analysis. These markers divided the signals on each channel of the 21 electrodes placed on the scalp into 10 frequency components between 4.68Hz and 18.72Hz. Each sNAT marker had 210 submarkers in total. In this coordinate space with 210 dimensions, the distance between the average coordinate point in the AD group and the individual coordinate point of each subject was represented by one number ($0 \leq n \leq 1$). The sNAT markers are considered useful for evaluating the (relative) overall balance of each site and frequency.

In this study, we calculated the "AD-NLc differential similarity", that is, a numerical index of the NAT marker to reflect its proximity to the NLc group or the AD group. This differential similarity can be calculated by subtraction of the two values. One is the similarity of a subject with the NLc group and the other is the similarity of a subject with the AD group, and the differential similarity is quantified by a number ($-1 \leq n \leq 1$). A positive number indicates a high probability of AD. During the follow-up period, a negative number indicated a high probability that cognitive function had improved.[16]

Statistical analysis

Kolmogorov-Smirnov was used to test for normality, and Spearman's rank correlation coefficient to test for correlation. The Wilcoxon signed-rank test and a paired *t*-test was used to compare data before and after intervention. A P-value < 0.05 was defined to be statistically significant. IBM SPSS Statistics version 25.0 was used for the statistical analysis in this study.

RESULTS

Changes in test results after intervention

Table 2 shows "word-recognition" scores, a TDAS subitem, of patients scoring TDAS < 7 pts and TDAS ≥ 7 pts. Since exercise training is believed to increase hippocampus size and improve cognitive function,[12] we focused on "word-recognition" scores. Only 16 subjects took the TDAS test both before and after intervention. No significant difference was noted in either total TDAS score or "word-recognition" score in any subject after the intervention compared to baseline. In 12 subjects with total TDAS ≥ 7 points at the time of admission, although total TDAS score did not change after the intervention, a significant improvement was observed in the "word-recognition" score ($P < 0.05$). In the 4 subjects with TDAS < 7 pts(Normal Cognitive) at the time of admission, neither total TDAS score nor "word-recognition" score changed significantly after the intervention.

NAT markers in patients tested are shown in Table 3. In all subjects who could be tested, sNAT changed significantly after rehabilitation compared to before the intervention ($P < 0.05$).

Correlation between peri-interventional changes in TDAS scores and sNAT

Table 4 shows correlations between changes in TDAS scores before and after the intervention and those of the NAT marker before and after the intervention in the subjects eligible for the test. There was no significant correlation between changes in TDAS before and after the intervention and sNAT. However, among 10 subjects with possible cognitive impairment, a medium positive correlation was observed between changes in "word-recognition" before and after the intervention and sNAT ($r = 0.634$, $P < 0.05$). No correlation was observed between age and changes such as TDAS ($r = 0.197$, $P > 0.05$), "word-recognition" ($r = 0.364$, $P > 0.05$), and sNAT ($r = 0.146$, $P > 0.05$). Also, there was no correlation between before and after the intervention regarding subjects with TDAS ≥ 7 points.

Table 2. Changes in TDAS score after intervention

Test score	Before intervention	After intervention	*P*-value
Total (n = 16)			
Total score	12.0 (7.5–17.5)	12.5 (5.0–15.8)	0.102
Word-recognition	5.5 (2.5–7.5)	5.0 (3.0–8.5)	0.058
TDAS < 7 (n = 4)			
Total score	3.0 (1.5–4.5)	1.0 (0.0–7.5)	1.000
Word-recognition	1.5 (1.0–2.0)	1.0 (0.0–6.0)	1.000
TDAS ≥ 7 (n = 12)			
Total score	13.0 (11.5–21.0)	13.5 (9.5–16.5)	0.059
Word-recognition	7.0 (5.0–12.5)	5.5 (4.0–10.0)	0.019*

Score are presented as median (Inter Quarter Range); *: $P < 0.05$. TDAS, Touch Panel-type Dementia Assessment Scale.

Table 3. Changes in sNAT after intervention

Test item	*n*	Before intervention	After intervention	*P*-value
sNAT	17	0.044 ± 0.084	0.006 ± 0.068	0.022*

Data presented as means ± SD; *: $P < 0.05$. sNAT, normalized power ratio index of Neuronal Activity Topography.

Table 4. Correlation between peri–interventional changes in TDAS score and sNAT

Test item	All		TDAS < 7		TDAS ≥ 7	
	n	*r*	*n*	*r*	*n*	*r*
Total score *vs* sNAT	14	–0.236	4	–0.400	10	–0.165
Word-recognition *vs* sNAT	14	0.375	4	–0.105	10	0.634*

*: $P < 0.05$. sNAT, normalized power ratio index of Neuronal Activity Topography; TDAS, Touch Panel-type Dementia Assessment Scale.

DISCUSSION

Total TDAS scores did not change significantly after the intervention in any participant in this study. However, the sub-item "word-recognition" improved significantly after intervention in subjects with decreased cognitive function, suggesting recent memory function may have improved at the time of discharge. Subjects with normal cognitive function at the time of admission maintained cognitive function that they had before hospital discharge. This could be due to the extremely small size of sample and ceiling effect. It has been reported that older adults who are hospitalized have significantly more risk of dementia after hospital discharge than those who weren't hospitalized.[23] Therefore, the possibility for them to have avoided Hospitalization-Associated Disability can't be denied.

The fact that the sNAT differential similarity, a marker of NAT, decreased significantly after intervention suggests that EEG patterns became closer to normal after rehabilitation. Changes in frequencies, amplitudes, and spatial coherence of EEG are mainly induced by alterations in neurotransmitters.[24] For example, since acetylcholine is decreased in the brain cortex of a patient with dementia,[25] drugs that increase the concentration of acetylcholine are currently prescribed for the treatment of dementia. Previous studies have shown exercise increases acetylcholine, even in older people.[14] Since association between cognitive function and EEG was shown, we thought that acetylcholine acted on cognitive function and EEG. Effect of rehabilitation on cognitive function might have been caused by multiple factors including neurotransmitters and neurotrophic factors besides acetylcholine[13] as well as by the improvement of cerebral blood flow.[14] If the shift towards normalization confirmed before and after the intervention was caused due to rehabilitation, continuing the same level of exercise during hospital stay will become important even after hospital discharge.

Limitations of our study are as follows. First, we could not prepare a control group. Patients are hospitalized after fracture to receive rehabilitation to recover physical function and improve mobility needed for their daily life activities to return to their home or social roles as soon as possible, so in fact, all patients would prefer to receive rehabilitation. Secondly, the target was not a single disease entity; we enrolled both hip and vertebral

fractures. Lastly, the length of hospital stays varied with a limited number of cases.

However, our findings suggest EEGs in patients with fractures resulting from a fall became more similar to NL patterns at the time of discharge. In addition, recent-memory function of patients who had a decline in cognitive function improved. There was no special treatment done to subjects of this study during hospitalisation except for the rehabilitation for ADL recovery.

Although this study was an open-label study and we could not prove the effectiveness of rehabilitation, we were able to obtain results that could be expected to be effective. We would like to collect enough cases in the future to design controlled trials and examine the effects of rehabilitation on cognitive function.

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The authors declare no conflict of interest.

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